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Periodic breathing is commonly seen during sleep in healthy humans following ascent to high altitude. The hyperventilation induced by hypoxia at altitude leads to hypocapnia which can, during sleep, inhibit respiration yielding apnea. The subsequent fall in PO_2 and rise in PCO_2 could then trigger hyperventilation and perpetuate the cycle. This cycling requires sufficient hyperventilation in response to hypoxia and rising PCO_2 to produce the necessary level of hypocapnia. As a result, these events may be influenced by inter-individual variability in the hypoxic and hypercapnic ventilatory response. To test this theory, we

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measured hypoxic (HVR) and hypercapnic (HCVR) ventilatory responses awake and NREM sleep both at sea level and on nights 1, 4, and 7 following arrival at altitude (14,110 ft) in six healthy males. Ventilatory pattern and PCO_2 were also determined on these nights. On night 1 at altitude, periodic breathing developed in three of the six subjects and correlated significantly with the sea level NREM HVR (r=.86, P=.02), and near-significantly with both the sea level awake HVR (r=.83, P=.08), and sea level NREM HCVR (r=.76, P=.08). Periodic breathing decreased on nights 4 and 7, but an association persisted between the number of respiratory oscillations and the NREM hypercapnic response determined on the respective night (night 4, r=.93, P=.02; night 7, r=.89, P=.04). With this decrease in periodic breathing noted with acclimatization, greater hypocapnia (lower PCO_2) was required to inhibit ventilation (decreased apnea threshold) than was observed early at altitude. These findings suggest that high ventilatory chemoresponsiveness is important in producing ventilatory instability at altitude and that with acclimatization periodic breathing may decrease in part related to shifts in the apnea threshold.

RE: Missing Figures
No figures are available for this report.
Per Ms. Debbie Longley, ARIEM

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April 28, 1986

Allen Cymerman, Ph.D.
U.S. Army Research Institute
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Natick, MA 01760

Dear Allen:

Enclosed are the two articles related to the sleep studies obtained on Pikes Peak last summer. They have been submitted as companion articles to the Journal of Applied Physiology. I assume they are being reviewed at this time.

It was nice to see you and to hear of your "Everest II" undertaking at the FASEB Meeting. I hope all continues to go well for you.

Sincerely yours,

David

David P. White, M.D.
Assis. Professor of Medicine
Pulmonary Division

DPW:dls
Enclosure

TITLE: PREDICTORS OF PERIODIC BREATHING AT ALTITUDE

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ABBREVIATED TITLE: Predictors of Periodic Breathing

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ABSTRACT

Periodic breathing is commonly seen during sleep in healthy humans following assent to high altitude. The hyperventilation induced by hypoxia at altitute leads to hypocapnia which can, during sleep, inhibit respiration yielding apnea. The subsequent fall in P_{O_2} and rise in P_{CO_2} could then trigger hyperventilation and perpetuate the cycle. This cycling requires sufficient hyperventilation in response to hypoxia and rising P_{CO_2} to produce the necessary level of hypocapnia. As a result these events may be influenced by inter-individual variability in the hypoxic and hypercapnic ventilatory response. To test this theory, we measured hypoxic (HVR) and hypercapnic (HCVR) ventilatory responses awake and during NREM sleep both at sea level and on nights 1,4, and 7 following arrival at altitude (14,110 ft) in six healthy males. Ventilatory pattern and P_{CO_2} were also determined on these nights. On night 1 at altitude, periodic breathing developed in three of the six subjects and correlated significantly with the sea level NREM HVR ($r=.86$, $P=.02$), and near-significantly with both the sea level awake HVR ($r=.83$, $P=.08$), and sea level NREM HCVR ($r=.76$, $P=.08$). Periodic breathing decreased on nights 4 and 7, but an association persisted between the number of respiratory oscillations and the NREM hypercapnic response determined on the respective night (night 4, $r=.93$, $P=.02$; night 7, $r=.89$, $P=.04$). With this decrease in periodic breathing noted with acclimatization, greater hypocapnia (lower P_{CO_2}) was required to inhibit ventilation (decreased apnea threshold) than was observed early at altitude. These findings suggest that high ventilatory

chemoresponsiveness is important in producing ventilatory instability at altitude and that with acclimatization periodic breathing may decrease in part related to shifts in the apnea threshold.

Index Words: Hypoxic and Hypercapnic Ventilatory Responses, Acclimatization, Apnea Threshold, Periodic Breathing.

INTRODUCTION

That periodic breathing during sleep in healthy humans follows ascent to high altitude has been observed for many years (7,23). Similar events are also known to occur with hypoxia induced in the laboratory at sea level (13). Recently, investigators have outlined the mechanisms which may, in part, explain this periodic breathing (2,4,5). One important contributor to these respiratory oscillations is the interaction between hypoxia and hypocapnia. The hyperventilation induced by hypoxia leads to hypocapnic alkalosis which can suppress respiration [apnea threshold(21)]. Subsequent apnea or hypopnea leads again to arterial hypoxemia and a rising P_{CO_2} which stimulate hyperventilation and complete the cycle. This sequence, however, requires that adequate hyperventilation and subsequent hypocapnia will develop in response to hypoxia (and possibly hypercapnia) to ultimately inhibit ventilation. If this does not occur, ventilation is unlikely to cycle.

The occurrence of periodic breathing at altitude is highly variable being marked in some and absent in others (16,19,23). The explanation for this is incompletely understood, but may relate to individual variability in hypoxic sensitivity. If the sequence of hypoxia-hypocapnia-apnea described above is correct, we would expect an individual with high hypoxic sensitivity to have considerable periodic breathing and that there would be less cycling in those with lower drives. However, previous studies have not consistantly confirmed this relationship between chemosensitivity and periodic breathing (23). This may be

attributable to the fact that the ventilatory responses to chemical stimuli in this study were measured during wakefulness which may not be a good indicator of the responses during sleep.

It has also been observed that periodic breathing diminishes with time at moderate altitude (19). This observation remains unexplained and is somewhat surprising as ventilation and hypocapnia increase during the initial days of hypoxic exposure both awake and asleep (3,12) which should increase periodic breathing. Several explanations seem possible. First, the apnea threshold could shift to lower P_{CO_2} levels than are reached during sleep thus preventing apnea despite progressive hyperventilation. Alternatively, hypoxic sensitivity could be reduced with acclimatization. This could be a product of the acclimatization process itself or result from diminished gain of the carotid body secondary to the improved oxygenation occurring with time at altitude. Although previous studies suggest that the hypoxic ventilatory response does not diminish and may even increase with acclimatization (6,11), the explanation for the decrement in periodic breathing remains obscure.

To help answer these questions, we measured respiratory pattern and ventilatory chemical responsiveness awake and asleep at sea level and over time at altitude in six healthy males. We also determined the influence of altitude acclimatization on the apnea threshold during periodic breathing.

METHODS

Six healthy males were studied; their physical characteristics being outlined in Table 1. None were obese,

smoked cigarettes, or had any current medical problems. All were also without sleep complaints and none had snored in the past or while being studied. The sea level studies were completed in Hershey, Pennsylvania (altitude: 350 feet, barometric Pressure: 750 mmHg) and the high altitude protocols on Pikes Peak (altitude 14,110 ft, Barometric Pressure: 460 mm Hg) at the U.S. Army Medical Research Facility.

Equipment

For the most part identical equipment was used at both study sites. All studies were conducted using a sealed face mask with one-way inspiratory and expiratory ports and sampling sites for end-tidal gas determinations. With an inflatable face cushion, the mask had a dead space of 75-85 ml depending on facial configuration. Attached around the entire circumference of the face cushion was a catheter with multiple sampling ports. This catheter was connected to an infrared CO_2 analyzer (Beckman Instruments, Anaheim, CA) set at maximum gain thus serving as a leak detector capable of determining an expiratory leak of approximately 1.2% of total ventilation when tested in a closed system (9). End-tidal P_{CO_2} ($P_{ET}CO_2$) was measured with a second infrared CO_2 analyzer (Beckman Instruments), and ventilation with a hot wire anemometer (Thermo Systems Incorporated, St. Paul, Minn). The CO_2 analyzer was calibrated with a gas mixture whose concentrations were determined by the Scholander technique (20). The flowmeter was originally calibrated with rotometers and frequently checked against a Tissot apparatus. Arterial oxygen saturation was measured at sea

level with a Biox II ear oximeter (Biox Inc. Boulder, CO) and at altitude with a Hewlett Packard instrument (Model 47201A, Waltham, MA).

The signals from the CO_2 analyzer ($P_{ET}CO_2$), anemometer ($\dot{V}_E$), and oximeter (SaO_2) were fed into a Data General Nova 4 computer (Data General, Westboro, Ma) which produced real-time analysis of these measurements. Sleep was staged (18) using standard silver cup electrodes for electroencephalography (EEG), electro-oculography (EOG), and electromyography (EMG). All sleep staging, leak, flow, $P_{ET}CO_2$, EKG, and oxygen saturation signals were recorded on a Grass Model 78D Polygraph (Grass Instruments, Quincy, MA).

Techniques

I Respiratory Pattern:

During sleep, at sea level and altitude, ventilatory pattern was determined by recording the flow and CO_2 signal on the polygraph. This allowed for breath to breath $P_{ET}CO_2$ measurements and continuous hard copy monitoring of respiratory pattern.

II Hypoxic Ventilatory Response (HVR):

All hypoxic ventilatory response testing will be reported as the slope of increasing ventilation versus decreasing arterial oxygen saturation.

A. Sea Level Awake:

Hypoxic responses were measured using a previously described technique (24). After breathing a hyperoxic mixture

(40% O_2, 60% N_2), the subject's arterial oxygen saturation was reduced to approximately 75% over 6-8 minutes by the addition of 100% nitrogen to the inspired mixture. End-tidal P_{CO_2} was maintained within 2mm Hg of the resting level by the addition of CO_2 to the inspired air.

B. Sea Level Asleep:

The procedure was identical to that described above except that the sleeping hypoxic studies were measured without CO_2 addition. This was done to mimic conditions at altitude. As a result $P_{ET}CO_2$ fell during all studies. We describe these studies as poikilocapnic to indicate that P_{CO_2} is changing, ie falling. All studies were conducted during NREM (stages 2,3, and 4) sleep with no REM studies being attempted. For inclusion in data analysis the following criteria had to be fulfilled: (a) no mask leak was detectable; (b) $Sa0_2$ was reduced to 80% or less without arousal; and (c) no stage change occurred from NREM to REM sleep. As many studies as possible were obtained with the only limitation being the disturbance of sleep.

C. Altitude Awake:

At altitude the oxygen content of the inspired gas was increased to produce an arterial oxygen saturation of 99 to 100% and the hypoxic respose was then measured as described for sea level. These studies were conducted isocapnically at the $P_{ET}CO_2$ level observed while the subject breathed the hyperoxic mixture. This was generally about 2 Torr higher than the eupnic $P_{ET}CO_2$ while breathing ambient air. Again the saturation was reduced to approximately 75% during these studies.

III Hypercapnic Ventilatory Responses (HCVR):

The hypercapnic ventilatory response was measured in the same manner awake and asleep, at altitude and at sea level. The subjects rebreathed from a bag containing ambient air with no CO_2 initially present. To conduct these studies at a constant SaO_2, small quantities of 95% O_2 - 5% CO_2 were added to the rebreathing bag to compensate for O_2 consumption and keep the SaO_2 within 3% of the baseline (ambient) values. The relationship between $P_{ET}CO_2$ and $\dot{V}_E$ is linear, and the data were analyzed by a least squares regression. The equation used to relate ventilation and $P_{ET}CO_2$ is $\dot{V}_E = S(P_{ET}CO_2-B)$, where B is the extrapolated intercept on the axis and S is the slope of the line expressed as change in ventilation per unit change in $P_{ET}CO_2$. During wakefulness at sea level and altitude, the $P_{ET}CO_2$ was elevated 10-15 mmHg above the resting level to define the hypercapnic response. This was not always possible during sleep due to arousal. To be included in data analysis at sea level, the $P_{ET}CO_2$ during sleep had to rise at least 8 mmHg above the resting level. At altitude where hypercapnic responses were quite brisk under hypoxic conditions even an 8 mmHg increase in $P_{ET}CO_2$ could not be attained without arousal. Thus at altitude, we accepted a 4 mmHg rise in $P_{ET}CO_2$ and a doubling of ventilation. Such changes permitted accurate definition of the hypercapnic response. As previously stated, we excluded any study in which a mask leak was detected or when a sleep stage change occurred. As many hypercapnic responses as possible were conducted in each sleep stage with the only limitation being the disruption of sleep.

IV CO_2 and O_2 Addition:

At altitude, during the periodic breathing of NREM sleep, the effects of interventions on respiratory cycling were studied. First, to determine the effect of gradually increasing $P_{ET}CO_2$, the subject would be connected to a rebreathing circuit which allowed CO_2 to increase with SaO_2 held constant. The $P_{ET}CO_2$ level at which breathing became rhythmic was thus determined. Second, we studied the effect of increasing SaO_2 on periodic breathing. Oxygen was slowly added to the inspired gas mixture and the subsequent events observed. Particular attention was paid to apnea length and the SaO_2 and $P_{ET}CO_2$ levels at which breathing regularized. Again, these studies were conducted only during NREM sleep at altitude during periodic breathing.

Protocols:

Sea Level:

All subjects spent two complete nights in the sleep laboratory at sea level. The first night was for acclimatization only and although no data was collected the procedures were, in other respects, identical to the second night. On the second night the subject reported to the laboratory at his usual bed time having fasted for at least four hours. After monitoring equipment was connected, each subject lay in bed for twenty minutes before any data was collected. At that point a single hypoxic and then hypercapnic ventilatory response was determined during documented (EEG) wakefulness. The subject was then allowed to go to sleep. During sleep hypoxic and hypercapnic ventilatory responses were measured as often as possible in

isolated sleep stages. Finally, ventilatory pattern was recorded on the polygraph throughout the entire night to ensure that no subject had underlying sleep disordered breathing. After final awakening, a second awake hypoxic and hypercapnic ventilatory response were measured.

Altitude:

All subjects were studied on nights 1, 4, and 7 in the laboratory on Pikes Peak having arrived at the summit 4 to 6 hours prior to the first night study. At approximately 8 p.m. after no caloric intake for at least 2.5 hours, monitoring equipment was connected and the subjects lay quietly in bed for 20 minutes before data was collected. As at sea level, a single hypoxic and hypercapnic response were then determined during EEG-documented wakefulness. The subjects were then allowed to sleep.

Two subjects were studied each night in separate sleep rooms. A continuous recording of sleep staging signals (EEG, EMG, and EOG) throughout the night was generated on each subject but only one subject's ventilatory variables could be recorded at a time so recordings were made intermintantly on each subject. We generally monitored ventilation on the sleeping subject if only one was asleep. Using this method, we measured hypercapnic ventilatory responses repeatedly during isolated sleep stages (NREM and REM) during the night. Finally, during episodes of periodic breathing we added CO_2 and O_2 (separately as described) to the inspired air to regularize ventilation. For substantial periods of time, ventilatory pattern was monitored in each

subject without intervention. As a result, a reasonably quantitative measure of periodic breathing could be obtained. To analyze respiratory oscillations, an interval exceeding five seconds without ventilation was considered a respiratory pause and reported as pauses/hour. This interval was selected as it represents a two-fold or greater increase in expiratory time over that seen during regular breathing and therefore exceeds expected cycle length.

Data Analysis:

Least squares linear regressions (22) were used to determine correlations between ventilatory responses to chemical stimuli and the frequency of periodic breathing.

RESULTS

With few exceptions (Table 1), all data were acquired in all subjects. It should be noted that subject 3 was not studied on nights 4 and 7 at altitude as he returned to sea level on day 3 following the development of high altitude pulmonary edema.

Periodic Breathing:

Ventilatory pattern was monitored for a mean interval of 2.5±0.2 hours per subject per night at altitude. Periodic breathing occurred in 3 of the 6 subjects and varied quantitatively between the three as is shown in Table 2. All periodic breathing occurred during NREM sleep. Although breathing was frequently erratic during REM sleep with variable tidal volume and frequency, no periodicity was evident. The frequency of respiratory periodicity decreased with time at altitude (Table 2) with little periodic breathing occurring by night 7.

Correlates of Periodic Breathing:

As can be seen in Table 3 and Figure 1, higher ventilatory responses to hypoxia and hypercapnia were associated with periodic breathing and lower responses were seen in those with regular breathing. The frequency of periodic breathing (pauses/hour) on night 1 at altitude correlated significantly with the sea level NREM poikilocapnic hypoxic response (r=.86, P=.02, Figure 1 and Table 3) and near significantly with both the awake sea level isocapnic hypoxic response (r=.83, P=.08) and the NREM sea level hypercapnic response (r=.76, P=.08). No determinants of chemoresponsiveness either awake or asleep obtained on the first night at altitude correlated with the quantity of periodic breathing seen that night. However, the number of pauses per hour of sleep on nights 4 and 7 at altitude correlated closely with the NREM hypercapnic ventilatory response obtained on the respective night (Table 3).

Influence of Alterations in Arterial Blood Gases on Periodic Breathing:

As can be seen in Table 2, only two subjects (subjects 1 and 2) had sustained periodic breathing at altitude. In both individuals the periodic breathing could be abolished by the addition of either CO_2 or O_2 to the inspired mixture (Figure 2 and 3). With CO_2 addition ventilation was regularized at a $P_{ET}CO_2$ within 1 mm Hg of the mean NREM $P_{ET}CO_2$ (Table 4 and Figure 3). This was generally 2 to 3.5 mmHg above the $P_{ET}CO_2$ recorded just prior to the respiratory pause (Table 4). With oxygen addition the respiratory pauses would initially lengthen

and then ventilation regularize, always at a $P_{ET}CO_2$ 2 to 4.5 mmHg higher than was required to produce rhythmic ventilation with CO_2 addition (Table 4 and Figures 2 and 3).

With acclimatization to altitude a number of changes occurred. First, periodic breathing steadily diminished with time at altitude (Table 2). Also, as can be seen on Table 4 and Figure 3, the apnea threshold ($P_{ET}CO_2$ prior to the respiratory pause) consistently decreased from night 1 to night 4 at altitude with little subsequent change thereafter. The $P_{ET}CO_2$ level necessary to regularize ventilation with either CO_2 or O_2 addition also shifted to a lower level between nights 1 and 4 at altitude (Table 4 and Figure 3). Therefore, with acclimatization a lower $P_{ET}CO_2$ must be achieved before an apnea or respiratory pause will occur and a lower $P_{ET}CO_2$ level is necessary to regularize ventilation.

DISCUSSION

This study suggests that there is a relationship between high ventilatory chemosensitivity and periodic breathing at altitude. Individuals with high hypoxic and hypercapnic ventilatory responses tend to have more marked periodic breathing than those with lesser responses. With time at altitude periodic breathing diminishes. This decrease in respiratory oscillations is associated with a reduction in the P_{CO_2} level necessary to inhibit ventilation.

Periodic breathing has been observed previously at altitude in individuals with widely variant awake hypoxic responses (23). However, no attempt was made to carefully correlate the frequency

of periodic breathing and chemoresponsiveness. Recently however, Lahiri et al (16) noted that Sherpas with low hypoxic sensitivity had little periodic breathing asleep while acclimatized lowlanders with higher hypoxic responses had frequent respiratory pauses. This suggests an important role for the hypoxic response in the development of sleeping respiratory oscillations. The ventilatory responses in that study, however, were measured during wakefulness which is likely an imperfect indicator of sleeping hypoxic sensitivity. Also sleep was never staged making it somewhat difficult to know exactly how much periodic breathing was occurring.

These observations may also improve our understanding of the previously reported absence of periodic breathing during REM sleep (2,23). As at sea level (8), the ventilatory response to hypercapnia at altitude was reduced 80% during REM sleep [see companion study (25)]. Although not measured at altitude, the hypoxic ventilatory response is also strikingly decreased during REM sleep at sea level (9). It would seem therefore that the ventilatory response to acute changes in P_{O_2} and P_{CO_2} may be insufficient during REM sleep to produce adequately increased ventilation and subsequent hypocapnia to trigger respiratory oscillations. However, it is possible that ventilation during REM sleep is heavily affected by "behavioral influences" (17) and that the previously described mechanisms producing periodic breathing during NREM sleep do not apply.

These findings are consistent with perviously formulated theories concerning the origin of periodic breathing.

Koo et al (15) in their mathematical model of periodic breathing beleived a high "loop-gain" was necessary to maintain respiratory oscillations. Increased ventilatory responses to hypoxia and hypercapnia can produce such a state. This has also been recently emphasized by Cherniack (4,5) who suggestes that increased "controller gain" can decrease the stability of the respiratory control system and produce respiratory oscillations. However, it has not been well demonstrated previously that intra-individual variation in hypoxic and hypercapnic sensitivity within the normal range can influence breathing pattern during sleep as our study suggests.

Two observations in the present study were somewhat surprising. First, no measure of chemosensitivity determined on the first night at altitude awake or asleep was a good predictor of periodic breathing on that night. This could be a product of the greater hypocapnia occurring at altitude in subjects with high hypoxic sensitivity. This hypocapnia could have reduced the measured response to isocapnic hypoxia at altitude thus confusing our determinations. However, this arguement is not particularly convincing and this observation must go unexplained. Secondly, the fact that three of our subjects had little or no periodic breathing is surprising as most investigators report respiratory oscillations during sleep at altitude in a clear majority of subjects studied (2,19,23). Two explanations seem plausible. Several of our subjects had hypoxic ventilatory responses at the low end of the normal range. In addition, the use of masks was required to collect the desired

data during sleep. Despite a low dead space, this may have increased the inspired CO_2 concentration and regularized ventilation in some individuals. However, the mask dead space was only 75 to 85 ml and the inspired CO_2 concentration always <0.5%. Although the increases in P_{CO_2} required to regularize breathing may be quite small, these studies were conducted to illustrate the influence of variation in ventilatory drives on periodic breathing which we believe was accomplished.

The fact that periodic breathing decreased with acclimatization has been described previously but never explained (19). This decrement in respiratory oscillations during sleep is certainly not a product of diminished chemosensitivity as the ventilatory responses to hypoxia and hypercapnia were either unchanged or increased with acclimatization [see companion article (25)]. We did note, however, that the P_{CO_2} level prior to an apnea (apnea threshold) diminished with time at altitude (Table 4 and Figure 3) as did the P_{CO_2} level necessary to regularize ventilation (Figure 3). This may be analogous to the progressive left shift (to lower P_{CO_2}) of the $\dot{V}_E$-P_{CO_2} relationship which is a well documented feature of acclimatization. It would seem that greater hyperventilation is necessary to reach the apnea threshold with acclimatization and that this does not occur as regularly after one has been at altitude for several days. This failure to hyperventilate adequately to produce hypocapnia and subsequent apnea following acclimatization is likely to be multifactorial. First, a greater increase in ventilation is

necessary to produce the same decrement in P_{CO_2} as the P_{CO_2} decreases. The stimulus to breathing during sleep may be inadequate to produce this level of ventilation. In addition, with acclimatization arterial oxygen saturation increases (3,25). As a result the individual is breathing on a flatter portion of the hypoxic ventilatory response and may have less stimulus to breathe with small changes in P_{O_2}. However, this effect may be offset by the increasing hypoxic sensitivity seen with acclimatization (25).

At higher elevations (5400 meters) investigators have noted periodic breathing to persist despite acclimatization (16). This is likely a product of two factors. First, at extreme altitude, severe hypoxia persists despite acclimatization and the individual continues breathing on the steep portion of the hypoxic ventilatory response. Second, the level of hypocapnia at high altitude is greater than at lower elevations and may be sufficient to inhibit ventilation despite acclimatization.

As described by others previously (2), we were able to regularize ventilation during sleep with the addition of either carbon dioxide or oxygen (Fig 2 and 3). In both cases ventilation became rhythmic as the P_{CO_2} level increased (Table 4 and Figure 3). This suggests that it is primarily hypocapnia and not hypoxia that is producing this respiratory cycling as outlined by Berssenbrugge(2). However, we noted that with O_2 addition, the P_{CO_2} level necessary to regularize ventilation was higher than was found with CO_2 addition (Table 4 and Figure 3). This suggests that hypoxia and hypercapnia may be

interactive in stimulating regular breathing at altitude. Apnea frequency and duration may be a product of both the hypoxic and hypercapnic responses as P_{CO_2} is increasing and P_{O_2} decreasing during these respiratory pauses. Thus with CO_2 addition, the hypoxic ventilatory stimulus persists and a lower P_{CO_2} level is necessary to inhibit ventilation. With O_2 addition, this hypoxic stimulus is abolished and a higher P_{CO_2} level is necessary to stimulate and regularize respiration.

In assessing our findings several potential weaknesses of the methods must be considered. First, a mask was employed to determine ventilation. Numerous recent studies suggest that the equipment (mask, mouthpiece) used to measure breathing can actually alter ventilation or its pattern (1,14). However, this seems to be a greater problem with a mouthpiece than a mask, and there are no indications that the sleep induced changes in respiration are affected by a mask. In fact, the basic trends in ventilation during sleep are quite similar whether a mask (10) or inductive plethysmograph (2,3) is used. In this study, a mask seemed the least obtrusive method of obtaining good quality data.

Another potential weakness of this study that needs to be asessed is the quality of sleep that can be obtained with the monitoring equipment employed. It seems unlikely that a normal night's sleep occurred during our investigation, particularly at altitude. However, the hypercapnic ventilatory responses were obtained in stable isolated sleep stages and are likely to reflect the physiologic condition in that stage. We were also

able to obtain enough undisturbed sleep at altitude, a mean of over 2 hours per subjects per night, to obtain a reasonably quantitative assessment of periodic breathing. Therefore, although sleep was certainly not undisturbed, it was sufficiently normal to obtain meaningful information.

We conclude that periodic breathing during NREM sleep at altitude occurs more frequently in individuials with high hypoxic and hypercapnic ventilatory responses than in subjects with lower ones, and rarely during REM sleep where reduced chemosensitivity is present (8,9,25). However, with time at altitude, periodic breathing decreases despite documented increasing hypocapnia and hypoxic sensitivity (25). This may be related to shifts in the apnea threshold (P_{CO_2} level necessary to inhibit ventilation) to lower values and the improved oxygenation seen with acclimatization.

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The views, opinions, and/or findings contained in this report are those of the authors and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation.

REFERENCES:

1. Askanazi J, PA Silverberg, RJ Foster, AI Hyman, J Milic-Emili, and JM Kinney. Effects of respiratory apparatus on breathing pattern. J Appl Physiol 48:577-580, 1980.

2. Berssenbrugge A, J Dempsey, C Iber, and J Skatrud. Mechanisms of hypoxia-induced periodic breathing during sleep in humans. J Physiol London 343:507-524, 1983.

3. Berssenbrugge AD, JA Dempsey, and JK Skatrud. Effects of sleep state on ventilatory acclimatization to hypoxia in humans. J Appl Physiol 57:1089-1096, 1984.

4. Cherniack NS. Respiratory dysrhythmias during sleep. N Engl J Med 305:325-330, 1981.

5. Cherniack NS. Sleep apnea and its causes. J Clin Invest 73:1501-1506, 1984.

6. Cruz JC, JT Reeves, RF Grover, JT Maher, RE McCullough, A Cymerman, and JC Denniston. Ventilatory acclimatization to high altitude is prevented by CO_2 breathing. Respiration 39:121-130, 1980.

7. Douglas CG, JS Haldane, Y Henderson, and EC Schneider. Physiological observations made on Pike's Peak, Colorado, with special reference to adaptations to low barometric pressures. Phil Trans Roy Soc Ser B 203:185-381, 1913.

8. Douglas NJ, DP White, CK Pickett, JV Weil, and CW Zwillich. Hypercapnic ventilatory response in sleeping adults. Am Rev Respir Dis 126:758-762, 1982.

9. Douglas NJ, DP White, JV Weil, CK Pickett, RJ Martin, DW Hudgel, and CW Zwillich. Hypoxic ventilatory response decreases during sleep in man. Am Rev Respir Dis 125:286-289, 1982.

10. Douglas NJ, DP White, JV Weil, CW Zwillich. Respiration during sleep in normal man. Thorax 37:840-844, 1982.

11. Forster HV, JA Dempsey, ML Birnbaum, WG Reddan, J Thoden, RJ Grover, and J Rankin. Effect of chronic exposure to hypoxia on ventilatory response to CO_2 and hypoxia. J Appl Physiol 31:586-592, 1971.

12. Gautier H, J Milic-Emili, G Miserocchi, and NM Siafakas. Pattern of breathing and mouth occlusion pressure during acclimatization to high altitude. Respir Physiol 41:365-377, 1980.

13. Gothe B, MD Goldman, NS Cherniack, and P Mantey. Effect of progressive hypoxia on breathing during sleep. Am Rev Respir Dis 126:97-102, 1982.

14. Hirsch JA and B Bishop. Human breathing patterns on mouth piece or face mask during air, CO_2, or low O_2. J Appl Physiol 53:1281-1290, 1982.

15. Koo MCK, RE Kronauer, KP Strohl, and AS Slutsky. Factors inducing periodic breathing in humans: a general model. J Appl Physiol 53:644-659, 1982.

16. Lahiri S, K Maret, and MG Sherpa. Dependence of high altitude sleep apnea on ventilatory sensitivity to hypoxia. Respir Physiol 52:281-301, 1983.

17. Phillipson EA. Control of breathing during sleep. Am Rev Respir Dis 118:909-939, 1978.

18. Rechschaffen A and A Kales. A manuel of standarized terminology, techniques, and scoring system for sleep stages of human subjects. Bethesda National Institute of Neurological Disease and Blindness, 1968. (NIH Publication No 204).

19. Reite M, D Jackson, RL Cahoon, and JV Weil. Sleep physiology at high altitude. Electroencephal Clin Neurophysiol 38:463-471, 1975.

20. Scholander PF. Analyzer for accurate estimation of respiratory gases in one half cubic centimeter samples. J Biol Chem 167:235-250, 1947.

21. Skatrud JB and JA Dempsey. Interaction of sleep state and chemical stimuli in sustaining rhythmic ventilation. J Appl Physiol 55:813-822, 1983.

22. Steele RG and JH Torrie. Principals and procedures of statistics. McGraw Hill, New York 1960.

23. Weil JV, MH Kryger, and CH Scoggin. Sleep and breathing at high altitude. In: Sleep Apnea Syndromes, edited by C. Guilleminault and WC Dement. New York: Liss, 1978, p119-135.

24. Weil JV, E Byrne-Quinn, IE Sodal, WO Friesen, B Underhill, GF Filley, RF Grover. Hypoxic ventilatory drive in normal man. J Clin Invest 49:1061-1072, 1970.

25. White DP, K Gleeson, CK Pickett, JT Reeves, AM Rannels, A Cymerman, and JV Weil. Altitude acclimatization (ventilation and chemoresponsiveness) during wakefulness and sleep. J Appl Physiol - Submitted

TABLE 1

Physical Characteristics of Subjects and Missing Data

Subject	Age	Ht (cm)	Wt (kg)	Missing Data
1	20	161	55.0(84.6)*	All data acquired.
2	22	175	82.3(113.1)	All data acquired.
3	23	193	89.5(105.3)	Sea level awake hypoxic responses. Night 1 altitude REM HCVR - No data for nights 4 and 7 at altitude.
4	23	177	62.6 (84.5)	All data acquired.
5	23	164	66.8(101.3)	Sea level REM hypercapnic response.
6	24	178	74.1 (99.9)	All REM studies on nights 1 and 7 at altitude.
Mean ± SEM	22.5 0.6	174.7 4.7	71.7 (98.1) 5.2	

* The number in parenthesis is the percent of ideal body weight.

TABLE 2

Periodic breathing at sea level and altitude

RESPIRATORY PAUSES PER HOUR

Subject	Sea Level	Night at Altitude 1	4	7
1	0	40.2	16.9	4.9
2	0	78.6	42.5	30.1
3	0	8.4	-	-
4	0	0.7	0.0	0.0
5	0	0.0	2.6	0.6
6	0	1.5	0.0	0.0
MEAN ± SEM	0	21.6 ± 13.0	12.4 ± 8.2	7.1 ± 5.8

A respiratory pause was defined as five seconds or more without ventilation.

TABLE 3

The Correlation Between Ventilatory Chemoresponsiveness and Periodic Breathing at Altitude

Respiratory Pauses/Hour on Night 1 at Altitude	r	P	Respiratory Pauses/Hour on Night 4 at Altitude	r	P	Respiratory Pauses/Hour on Night 7 at Altitude	r	P
Sea Level AWAKE Hypoxic Response	.83	.08	----------			----------		
Sea Level NREM Hypoxic Response	.86	.02	----------			----------		
Sea Level NREM Hypercapnic Response	.76	.08	----------			----------		
1st Night Alt. AWAKE Hypoxic Response	.55	.26	4th Night Alt. AWAKE Hypoxic Response	.79	.11	7th Night Alt. AWAKE Hypoxic Response	.04	.94
1st Night Alt. NREM Hypercapnic Response	.46	.35	4th Night Alt. NREM Hypercapnic Response	.93	.02	7th Night Alt. NREM Hypercapnic Response	.89	.04

TABLE 4

The Influence of Altitude Acclimatization on P_{CO_2} and Periodic Breathing

	Mean NREM		Pre Apnea		Post Apnea		VENTILATION REGULARIZED BY CO_2 Addition at		VENTILATION REGULARIZED BY O_2 Addition at	
SUBJECT 1	PCO_2	SaO_2	PCO_2	SaO_2	PCO_2	SaO_2	PCO_2	SaO_2	PCO_2	SaO_2
Night 1	35.1	77.8	32.8	75.9	36.8	82.4	35.0	77.3	38.0	95.0
Night 4	32.4	83.5	29.2	82.6	32.8	87.0	32.0	85.8	36.4	96.0
Night 7	32.9	86.2	----		----	----	----	----	----	----
SUBJECT 2										
Night 1	34.2	75.8	31.4	72.3	34.6	80.5	35.0	74.0	37.5	94.0
Night 4	32.8	79.3	30.7	74.1	33.7	84.1	33.8	76.3	36.2	96.3
Night 7	32.9	81.6	30.5	78.4	33.9	86.7	34.0	79.0	36.0	97.0

The P_{CO_2} (end-tidal P_{CO_2}) values are again in mmHg and the SaO_2 (arterial oxygen saturation) in percent.

FIGURE LEGENDS:

Fig 1 The relationship between respiratory pauses (>5 seconds) per hour on the first night at altitude and measures of hypoxic ventilatory response at sea level, awake and asleep, are shown. The awake hypoxic response was measured isocapnically and the NREM responses without CO_2 control (poikilocapnic).

Fig 2 Routine periodic breathing and regularization of ventilation by CO_2 addition and O_2 addition in Subject 1 on night 1 at altitude are shown. As can be seen, ventilation regularized with O_2 addition at a $P_{ET}CO_2$ value considerably higher than with CO_2 addition. Also the respiratory pauses are longer with O_2 addition than were seen during routine ventilation. $P_{ET}CO_2$, End-tidal P_{CO_2}; SaO_2, arterial oxygen saturation.

Fig 3 The relationship between arterial oxygen saturation (SaO_2) and P_{CO_2} in the development of periodic and regular breathing is demonstrated over the 7 nights at altitude in 2 subjects. The shaded regions indicate periodic breathing with the central point (in this shaded area) indicating the apnea threshold (P_{CO_2} level of the breath prior to a respiratory pause). The lines eminating from this apnea

threshold lead to the points at which ventilation was regularized following CO_2 and O_2 addition and the post-apneic blood gas value.